IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Viswanathan SRINIVASAN et al.

Confirmation No. 4898
Group Art Unit: 1615

Appl. No: : 10/798,884

Examiner: Sasan, Aradhana

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For : DOSAGE FORM CONTAINING A MORPHINE DERIVATIVE AND ANOTHER DRUG

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Commissioner for Patents
U.S. Patent and Trademark Office
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401 Dulany Street
Alexandria, VA 22314

Sir:

This Appeal is from the Examiner's Final Rejection of claims 117-200 set forth in the Office Action mailed from the U.S. Patent and Trademark Office on December 22, 2011.

A Notice of Appeal in response to the December 22, 2011 Final Office Action was filed on April 23, 2012. A request for a one-month extension of time is being filed concurrently herewith.

The fee for filing an Appeal Brief in support of a Notice of Appeal was paid on April 2, 2011 when the first Appeal Brief was filed. Pursuant to MPEP 1204.01 the U.S. Patent and Trademark Office is hereby authorized to charge the difference between the current fee for an Appeal Brief and the fee effective on April 2, 2011 as well as any additional fees which may be deemed necessary for entering the present Appeal Brief to Deposit Account No. 50-5475.

The fee for a one-month extension of time is being paid concurrently herewith.

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I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Sovereign Pharmaceuticals, LLC of Fort Worth, Texas. The corresponding assignment from the inventors to Sovereign Pharmaceuticals, Ltd. was recorded in the U.S. Patent and Trademark Office on July 28, 2004 at REEL 015615, FRAME 0519. The change of name from Sovereign Pharmaceuticals, Ltd. to Sovereign Pharmaceuticals, LLC was recorded in the U.S. Patent and Trademark Office on March 5, 2010 at REEL 024039, FRAME 0536.

II. RELATED APPEALS AND INTERFERENCES

Appellants note that appeals are pending before the BPAI in copending application Nos. 11/012,267 (Appeal No. 2010-012511) and 11/102,726 (Appeal No. 2011-04015). Further, a Notice of Appeal was filed on June 29, 2012 in co-pending application No. 10/736,902. Claims of the instant application have been provisionally rejected on the ground of alleged obviousness-type double patenting over claims of all of these copending applications.

Appellants, Appellants' representative or the Assignee are not aware of any other prior and pending appeals, interferences or judicial proceedings which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. SUMMARY OF CLAIMED SUBJECT MATTER

A. Claim 117

Independent claim 117 is drawn to a pharmaceutical dosage form which comprises (a) a first drug which comprises at least one morphine derivative having antitussive activity and (b) at least one second drug. The plasma half-life of the at least one second drug differs from the plasma half-life of the first drug and the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of the period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 2, lines 4-9 from bottom and page 62, lines 3-8 of the present specification.

B. Claim 140

Independent claim 140 is drawn to bi-layered tablet which comprises a first layer and a second layer, the first layer comprising a first drug which comprises at least one morphine derivative having antitussive activity, and the second layer comprising at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines. The bi-layered tablet provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 80 % of the period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 3, line 6 from bottom to page 4, line 2 and page 64, lines 12-19 of the present specification.

C. Claim 159

Independent claim 159 is drawn to a pharmaceutical dosage form which comprises (a) a first drug which comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof and has a first plasma half-life and (b) at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines and has a second plasma half-life which differs from the first plasma half-life by at least about 3 hours. The dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 80 % of the period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 7, line 2 from bottom to page 8, line 8 and page 71, lines 4-12 of the present specification.

D. Claim 166

Independent claim 166 is drawn to a pharmaceutical dosage form which comprises (a) at least one first morphine derivative in a first form or layer and (b) at least one second morphine derivative which is different from the first morphine derivative in a second form or layer which is different from the first form or layer. The dosage form releases the at least one first morphine derivative over a different period and/or at a different rate than the at least one second morphine derivative.

See, e.g., page 8, lines 12-17 and 20-23, page 17, lines 8-12 and page 72, lines 1-5 and 10-12 of the present specification.

E. Claim 180

Independent claim 180 is drawn to a bi-layered tablet which comprises a first layer and a second layer, the first layer comprising a first drug which is selected from codeine and pharmaceutically acceptable salts thereof, and the second layer comprising at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines. The bi-layered tablet provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of the period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

See, e.g., page 3, line 6 from bottom to page 4, line 9 and page 12, lines 1-10 of the present specification.

IV. ARGUMENTS

A. Claims 117-119, 134-139, 166, 167 And 175-179 Are Not Rendered Obvious By FANARA

1. Summary of Rejection

The Examiner takes the position, *inter alia*, that the subject matter of present claim 117 would allegedly have been obvious to one of ordinary skill in the art in view of FANARA. In this regard, the rejection mainly relies on col. 2, lines 36-50 of FANARA where it allegedly is taught to simultaneously administer more than one active substance and combining the therapeutic effects of active substances with different pharmacokinetic profiles. The rejection asserts that "[i]n order to have the combined therapeutic effects of active substances, it would have been obvious to one with ordinary skill in the art that the period of therapeutic effectiveness of the first active substance would be coextensive with

the period of therapeutic effectiveness of the second active substance, especially if the two active substances are related to similar (antitussive) therapeutic activities." Page 5, second paragraph of the December 22, 2011 Final Office Action.

2. Traverse

Claims 117-119 and 134-139

Appellants respectfully submit that the Examiner's conclusions with respect to FANARA are based on hindsight. In particular, FANARA is concerned primarily with pharmaceutical compositions for the controlled release of active substances (see, e.g., title and col. 1, first paragraph of FANARA), not with the administration of different active substances in a single dosage form and for this reason alone, one of ordinary skill in the art has no reason to consult FANARA for guidance in the latter respect.

The passage of FANARA which the Examiner appears to primarily rely on, i.e., col. 2, lines 36-50, states (emphasis added):

> In parallel, it is increasingly therapeutically advantageous to be able to simultaneously administer by the oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration. *In the case where the same active substance is simultaneously administered for immediate release and for prolonged release, this makes it possible to rapidly release a sufficient dose of active substance to trigger the desired effect and to maintain this effect by a gradual and prolonged release of the same active substance.* In the case where an active substance is released immediately and another active substance is released gradually, this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles.

The Examiner appears to take the position that in view of the above passage one of ordinary skill in the art allegedly would have had an apparent reason to provide a dosage form which comprises two different active substances, one released immediately

after administration and the other one released gradually and regularly after administration, and releases the two active substances in such a manner that the plasma concentration of one active substance is within a therapeutic range over a period which is coextensive with at least about 70 % of the period over which the plasma concentration of the other active substance is within a therapeutic range.

It is noted that the above passage makes reference to active substances which have "very different pharmacokinetic profiles" and can be administered by means of the immediate/controlled release formulations of FANARA. However, FANARA does not explain what exactly is to be understood by the phrase "very different pharmacokinetic profiles". In this regard, it is pointed out that the term "pharmacokinetic profile" encompasses a wide range of properties of a drug.

For example, according to

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

(see EVIDENCE APPENDIX) the term "pharmacokinetic profile" is defined as "[t]he characteristics of a drug that determine its absorption, distribution and elimination in the body".

Appellants are unable to see that the fact that FANARA mentions that the immediate/controlled release combinations set forth therein make it possible to obtain combined therapeutic effects by means of two active substances which have very different absorption, distribution and elimination characteristics in the body allegedly renders it obvious to (prompts) one of ordinary skill in the art to use an immediate/controlled release combination for providing plasma concentrations in a therapeutic range of these two active substances in a way such that the therapeutically

effective period of one drug overlaps at least about 70 % of the therapeutically effective period of the other drug.

It further is submitted that the last sentence of the above passage must not be read in isolation but within the entire context of this passage and in particular, in the context of the preceding sentence (in italics). In particular, the preceding sentence is concerned with the scenario where there is a need for fast action of a particular drug, i.e., to get the plasma concentration of the drug into the therapeutic range as fast as possible in order to treat or alleviate the condition or symptom to be treated as fast as possible (accomplished by an immediate release composition) and to thereafter maintain a concentration of this (the same) drug within the therapeutic range for prolonged periods of time (accomplished by a sustained release composition).

The equivalent of this scenario when two drugs "having very different pharmacokinetic profiles" are used in a single dosage form would, for example, be the use a first drug that is suitable for rapidly alleviating the symptoms of a condition due to the fact that it can rapidly be absorbed by the body and can rapidly afford a plasma concentration within the therapeutic range (e.g., a decongestant) and is provided in an immediate release composition (i.e., the entire first drug is released at once), followed by the sustained release of a second drug that treats the cause of the condition (e.g., an antihistamine) but takes more time to be absorbed by the body and thus, is not suitable for providing rapid relief from the symptoms of the condition. It is apparent that with this scenario there is no need for any overlap between the periods of a plasma concentration within the respective therapeutic ranges of the rapidly acting first drug and the second

drug because once the second drug treats the cause of the condition the symptoms thereof will disappear and there is no longer a need to alleviate these symptoms with the first drug. In other words, the period of a therapeutic plasma concentration of the first drug needs to last only up to the time when the second drug has reached its therapeutic plasma concentration. Clearly, a significant overlap of these two periods would not serve any useful purpose at all.

A second, similar scenario in which two drugs "having very different pharmacokinetic profiles" are used in a single dosage form is the case where both the first and the second drug are suitable for treating or alleviating the same condition (having the same therapeutic effect), the first drug being fast acting (rapidly absorbed) but having a relatively short half-life (thereby requiring large amounts of drug for maintaining its therapeutic effect for extended periods of time) and the second drug being slowly absorbed by the body but having a relatively long half-life, thereby requiring only relatively small amounts of drug to be continuously released once a plasma concentration within the therapeutic range is reached. In this case too, there apparently is no need for any significant overlap between the periods of a therapeutic plasma concentration of the first drug and the second drug.

It further is pointed out that the above-cited passage of FANARA must also be considered and assessed in the context of the entire disclosure of FANARA.

For example, in lines 15-27 of col. 3, FANARA makes it clear that the contribution thereof to the art does not rest in the provision of dosage forms which provide immediate/controlled release of two different active substances but rather that

the disclosed invention consists in the provision of a new matrix composition for the controlled release part of corresponding dosage forms (and, primarily, for dosage forms which consist of only a single, controlled release composition), which matrix composition has certain advantages.

Specifically, the inventors of FANARA acknowledge that "orally administrable solid pharmaceutical compositions combining, in a single unit, a portion exhibiting immediate release and a portion exhibiting delayed release have been described" but allege that these compositions are difficult to make and are not available in the desired form for each and every active substance. It further is stated in FANARA that the controlled release matrix compositions disclosed therein "do not require excessive quantities of matrix excipients and allow regular and continuous release of active substances over periods of at least 12 hours."

Accordingly, one of ordinary skill in the art will understand that FANARA neither teaches nor suggests combined immediate/controlled release dosage forms which are different from the known dosage forms in any respect other than the composition of the matrix for the controlled release portion thereof.

Further, FANARA does not at all convey the impression that immediate/controlled release dosage forms are advantageous or even only suitable for each and every combination of two active substances. For example, in the passage from col. 5, line 39 to col. 6, line 26 FANARA states (emphasis added):

> According to a specific embodiment of the invention, the controlled-release pharmaceutical compositions according to the invention are used in combination with one or more pharmaceutical compositions allowing immediate release of active substances. When these two types of compositions are present in the same

unit, this makes it possible to obtain, in a single administration, both the immediate release of a first active substance and the prolonged release of the same or of a second active substance.

Accordingly, the present invention also relates to pharmaceutical compositions which can be administered orally, comprising

A. at least one layer comprising an active substance and excipients which allow immediate release of the said active substance after administration, and
B. at least a second layer which allows the controlled release of the same or of a second active substance, comprising the said same or second active substance, at least one matrix-type excipient and at least one alkalinizing agent.

[…]

Such combined pharmaceutical compositions can be prepared according to various methods known to persons skilled in the art.

More particularly, these combined pharmaceutical compositions may be provided in the form of a tablet in which at least one layer A is stuck to at least one layer B.

[…]

The multilayer tablets are particularly well suited to cases of combinations of active substances for which very specific beneficial therapeutic effects have recently been obtained, for example, pseudoephedrine/cetirizine, hydrocodone/acetaminophen, immediate release hydrocodone/prolonged release hydrocodone.

The embodiments referred to by FANARA in the last paragraph of the above passage are illustrated in Example 4 (double-layer tablet containing controlled-release pseudoephedrine and immediate release cetirizine) and Example 7 (double-layer tablet containing hydrocodone in both a controlled-release layer and an immediate release layer).

The fact that FANARA mentions only a few very specific examples of combinations of active substances for which the immediate/controlled release dosage forms (multilayer tablets) mentioned therein may be "particularly well suited" rather than pointing out that these multilayer tablets are advantageous with respect to the administration of any combination of two active substances is a clear indication that the

inventors of FANARA were not at all concerned about the overlap of the periods of therapeutic effectiveness of these active substances. This is further supported by, e.g., Table 10 in col. 10 of FANARA which compares the time-dependent release of the two active substances (pseudoephedrine and cetrizine) in the double-layer tablet of Example 4 but fails to provide any information whatsoever regarding the duration of action of these two active substances, let alone regarding the overlap in the periods of therapeutic effectiveness thereof.

At any rate, there is not even a single passage in FANARA wherein the duration of action of any active substance is addressed. Whenever combinations of active substances are mentioned in FANARA these combinations are to be contained in immediate release/controlled release dosage forms, i.e., dosage forms which are designed for the sole purpose of providing different release rates and/or release periods of the active substances, i.e., without any concern regarding the time and duration of action of one active substance in relation to the time and duration of action of the other active substance. This fact alone should make it apparent that FANARA is unable to render obvious the subject matter of claim 117, i.e., a claim which addresses, in terms of plasma concentrations within a therapeutic range, the relationship (overlap) between the time and duration of action (period of therapeutic effectiveness) of one particular type of drug (i.e., a morphine derivative having antitussive activity) and the time and duration of action of another (second) drug which is comprised in the same dosage form (and has a different plasma half-life than the morphine derivative).

Appellants further note that the Examiner has failed to provide any (written or other) evidence which shows that differences in release rates of different active substances from a single dosage form result in and/or are conventionally used to provide plasma concentrations in a therapeutic range of two active substances (with different plasma half-lives) present in the single dosage form over similar or substantially coextensive periods of time. In fact, the Examiner has not even cited to a single example of the use of different release rates (and in particular, a combination of immediate release and controlled release) for achieving similar or substantially coextensive periods of therapeutic activity of two different active substances, let alone of two different active substances which comprise a morphine derivative having antitussive activity and another active substance whose half-life differs from that of the morphine derivative.

It additionally must be taken into account that instant claim 117, for example, recites generally a combination of elements, *inter alia*,

(1) a pharmaceutical dosage form which comprises a first drug which comprises at least one morphine derivative having antitussive activity and at least one second drug (selected, e.g., from decongestants, expectorants, mucus thinning drugs, and antihistamines);

(2) a difference in the plasma half-lives of the first and second drugs; and

(3) an overlap of the periods within which the first drug and the at least one second drug show a therapeutic effect (i.e., an overlap of the periods within which the first drug and the at least one second drug provide a plasma concentration with the respective therapeutic ranges) of at least about 70 % (and up to at least about 95

%, see, e.g., claim 133).

In contrast, FANARA does not mention elements (2) and (3) at all and mentions element (1) merely in passing. Regarding elements (2) and (3) the rejection relies primarily on the general statement in col. 2, lines 36-50 of FANARA reproduced above.

The rejection essentially asserts that in view of the above statement in combination with the Examples of FANARA and in particular, Example 7 thereof (describing a double-layer tablet containing hydrocodone in both a controlled-release layer and an immediate release layer) it would have been obvious to one of ordinary skill in the art to provide a pharmaceutical dosage form which shows the combination of elements (1) to (3) set forth above. However, nothing in the above passages (or any other passage) of FANARA points to a dosage form which provides a plasma concentration within a therapeutic range of a first active substance and a plasma concentration within a therapeutic range of a second active substance over similar or substantially coextensive periods of time, respectively, let alone in a case where the plasma half-lives of these active substances are different.

Specifically, FANARA mentions exclusively immediate release/controlled release combinations, i.e., combinations which provide different release rates of the active substances (in this regard, see also Table 10 in col. 10 of FANARA which lists the time-dependent release of the drugs in the double-layer tablet of Example 4), but is completely silent with respect to the duration of action of the active substances, let alone the duration of action of one drug in relation to the duration of action of the other drug.

In this regard, Appellants point out that "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any

explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512, F.3d 1363, 1374 n.3 (Fed. Cir. 2008). "[I]t is not enough to simply show that the references disclose the claim limitations; in addition, 'it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does.'" *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc.*, 617, F.3d 1296, 1303 (Fed. Cir. 2010). Further, it is also necessary for the Examiner to properly construe what an applied reference *fairly* teaches or discloses. See, e.g., *In re Fracalossi and Wajer*, 681 F.2d 792 (CCPA 1982). Ultimately therefore, "[i]n determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir 1995) (internal quotations omitted).

Further, regarding the allegations and the graphs at page 7 of the December 22, 2011 Final Office Action, it is not clear to Appellants why the alleged different possible interpretations of claim 117 make any difference in the instant context.

It is submitted that these graphs and the accompanying allegations appear to be an indication that the Examiner has not completely understood the meaning and implications of the rejected claims. At any rate, these graphs and allegations illustrate even further the non-obviousness of the subject matter of the rejected claims.

For example, according to graph A ("Co-extensive plasma concentration") there is a measurable plasma concentration for both drugs over the same time period, i.e., from

time 0 to time 8. In other words, there is a 100 % overlap in the time periods over which these two drugs show a measurable plasma concentration. However, this overlap does not mean that there also is a 100 % overlap in the periods over which the drugs show plasma concentrations within the therapeutic ranges thereof.

In particular, if one were to assume, for example, that the minimum plasma concentration at which the first drug shows a therapeutic effect is 10, the plasma concentration within the therapeutic range for the first drug would be from time 1 to time 7, i.e., would span 6 time units. If one further were to assume that the minimum plasma concentration at which the second drug shows a therapeutic effect is 15, the plasma concentration within the therapeutic range for the second drug would be from time 2.5 to time 5.5, i.e., would span only 3 time units. Accordingly, despite the fact that both drugs show a 100 % overlap in the time periods over which their plasma concentrations are measurable, in this case the period over which the plasma concentration of the second drug is within the therapeutic range would be coextensive with only 50 % of the period over which the plasma concentration of the first drug is within the therapeutic range.

Accordingly, even if one of ordinary skill in the art were to select suitable formulations for two different drugs to ensure that both drugs, when ingested together, are present in a patient's plasma over substantially the same period, this would by no means guarantee that the periods over which these drugs show plasma concentrations within their therapeutic ranges overlap to a significant extent (as indicated in the rejected claims).

The above remarks should have made it apparent that the concept on which the present invention is based is much more sophisticated than is appreciated by the Examiner.

Claims 166, 167 and 175-179

Independent claim 166 essentially recites that the pharmaceutical dosage form set forth therein comprises at least two different morphine derivatives in two different forms or layers and that the dosage form releases these at least two different morphine derivatives at different rates and/or over different periods.

FANARA mentions a combination of immediate release hydrocodone and prolonged release hydrocodone in col. 6, lines 24/25 and illustrates in Example 7 thereof a double-layer tablet which comprises hydrocodone bitartrate in both an immediate release layer and a controlled release layer.

In comparison, instant claim 166 encompasses, *inter alia*, a combination which comprises (at least) two <u>different</u> morphine derivatives which are released at different rates and/or over different periods. FANARA neither teaches nor suggests that the hydrocodone in one of the layers of the double-layer tablet of Example 7 can or should be replaced by a <u>different</u> morphine derivative, and neither does the Examiner offer any explanation in this regard. For this reason alone, FANARA fails to render obvious the subject matter of present independent claim 166 (and any of the claims dependent therefrom) as well.

In view of the foregoing, it is submitted that the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter recited in present independent

claims 117 and 166 (and any of the claims dependent therefrom) with respect to FANARA.

B. Claims 120-123, 128-133, 140-153, 155-157, 159-165, 168-174, 180-195 And 198-200 Are Not Rendered Obvious By FANARA In View Of JAEGER

1. Summary of Rejection

The rejection appears to concede that FANARA alone does not render obvious the subject matter of the rejected claims but alleges that JAEGER cures the deficiencies of FANARA in this regard. Specifically, the rejection relies on Example 2 of JAEGER which allegedly illustrates a three-layer "pill" or tablet containing codeine phosphate. The rejection further asserts that JAEGER also teaches preparations which contain codeine and additional drugs such as antihistamines, decongestants and expectorants.

2. Traverse

Claims 120-123, 128-133, 140-153, 155-157, 159-165, 180-195 and 198-200

Appellants note that independent claims 140, 159 and 180 have in common with independent claim 117, *inter alia*, that they also recite a pharmaceutical dosage form (e.g., a bi-layered tablet) which comprises at least one morphine derivative having antitussive activity (e.g., codeine or a pharmaceutically acceptable salt thereof) and at least one second drug and provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % (e.g., at least about 80 %) of a period over which the dosage form provides a plasma concentration within a therapeutic range of the at least one morphine derivative.

As set forth above in section IV.A.2., FANARA is unable to render obvious a corresponding dosage form. It is not seen that JAEGER cures the corresponding deficiencies of FANARA, and neither does the Examiner provide any explanation in this regard.

Specifically, JAEGER teaches that 6-amino-2-methyl-2-heptanol (heptaminol), a relatively non-toxic compound lacking antitussive effects of its own, can enhance the effect of codeine so that the codeine dosage and the associated side effects may be reduced sharply while achieving a desired antitussive effect (col. 1, lines 11-17). Example 2 of JAEGER describes a three-layer pill wherein each of the layers contains both heptaminol and codeine phosphate. JAEGER also mentions that the compositions described therein may additionally contain antihistamines, expectorants and decongestants. In particular, in col. 3, lines 3-12, JAEGER states:

> Conventional cold preparations containing codeine may additionally contain antihistamines such as triprolidine hydrochloride, decongestants such as pseudoephedrine hydrochloride, and expectorants, such as glyceryl guaiacolate. 40 Percent of the codeine in such preparations may be replaced by heptaminol according to this invention without decreasing antitussive potency while reducing the side effects of the codeine. The heptaminol may benefit the patient by contributing its known physiological effects.

Appellants are unable to see that the above passage of JAEGER can render it obvious to combine codeine (phosphate) and an antihistamine, decongestant or expectorant in a dosage form (in particular, a bi-layered tablet) which provides the codeine and the second drug in such a way that the period of plasma concentration within a therapeutic range of the antihistamine, decongestant or expectorant is coextensive with at least about 70 % (or at least 80 %) of the period over which the plasma concentration of codeine is within a therapeutic range.

Appellants submit that for the above reasons alone, FANARA in view of JAEGER is unable to render obvious the subject matter of any of claims 120-123, 128-133, 140-153, 155-157, 159-165, 180-195 and 198-200.

Claims 168-174

Claims 168-174 are (ultimately) dependent from claim 166. As set forth above in section IV.A.2., FANARA is unable to render obvious the dosage form recited in claim 166. It is not seen that JAEGER cures the corresponding deficiencies of FANARA, and neither does the Examiner provide any explanation in this regard. For this reason alone, FANARA in view of JAEGER is unable to render obvious the subject matter of any of claims 120-123, 128-133, 140-153, 155-157, 159-165, 180-195 and 198-200.

Claim 159

What independent claim 159 has in common, *inter alia,* with independent claim 117 is that it also recites a pharmaceutical dosage form which comprises a first drug comprising at least one morphine derivative having antitussive activity (in particular, codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof) and at least one second drug (in particular, a drug selected from decongestants, expectorants, mucus thinning drugs, and antihistamines) whose period of plasma concentration within a therapeutic range is coextensive with at least about 70 % (in particular, at least about 80 %) of the period over which the plasma concentration of the first drug is within the therapeutic range. Compared to claim 117 claim 159 additionally recites that the at least

one second drug has a plasma half-life which differs from the plasma half-life of the first drug by at least about 3 hours.

As set forth above with respect to independent claim 117, FANARA fails to render it obvious to one of ordinary skill in the art to provide an (intermediate/controlled release) dosage form which releases two different drugs in such a way that the therapeutically effective period of one drug overlaps the therapeutically effective period of the other drug by at least about 70 %.

Further, as also set forth in detail above with respect to claims 120-123, 128-133, 140-153, 155-157, 159-165, 180-195 and 198-200, JAEGER is unable to cure the deficiencies of FANARA and for this reason alone, the subject matter of present claim 159 (and the claims dependent therefrom) is not rendered obvious by a combination of these two documents.

In addition, neither FANARA nor JAEGER addresses any plasma half-lives, let alone any difference in the plasma half-lives of two drugs which are combined in a single dosage form.

In view of the foregoing, it is submitted that the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of independent claim 159 and any of the claims dependent therefrom with respect to FANARA in view of JAEGER for these additional reasons as well.

Claims 128-130

Claims 128-130 all depend, directly or indirectly, from independent claim 117 and essentially recite, *inter alia*, that the plasma half-life of the at least one second drug

recited in claim 117 differs from the plasma half-life of the at least one first drug recited in claim 117 by at least about 2, 3 or 4 hours respectively.

The Examiner apparently concedes that FANARA by itself is unable to render obvious the subject matter of claims 128-130 but appears to take the position that JAEGER cures the deficiencies of FANARA in this regard.

Appellants submit that JAEGER is completely silent as to the plasma half-life of any drug mentioned therein (and so is FANARA), let alone mentions any difference between the plasma half-lives of two drugs. For this additional reason alone (i.e., in addition to the reasons set forth above), the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of present claims 128-130 over FANARA in view of JAEGER.

Claim 144

Claim 144 depends from claim 141, which in turn depends from independent claim 140 and essentially recites that the bi-layered tablet of claim 140 comprises (a) at least one morphine derivative having antitussive activity and (b) at least two of phenylephedrine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin, and pharmaceutically acceptable salts thereof as the at least one second drug.

Appellants fail to see that FANARA and/or JAEGER teaches or suggests corresponding drug combinations, let alone in combination with a disclosure (i) that the therapeutically effective periods of the drugs (b) are to overlap the therapeutically effective periods of drugs (a) by at least about 80 % (as recited in claim 140) and (ii) that not more than about 20 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the

plasma concentration of the first drug is within the therapeutic range (as recited in claim 141).

Appellants submit that for at least the foregoing reasons and the additional reasons set forth above, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of claim 144.

Claim 150

Claim 150 depends from independent claim 140 and recites that both layers of the bi-layered tablet of claim 140 are controlled release layers.

Appellants note that the disclosure of FANARA which relates to multi-layered tablets appears to be limited to combinations which comprise both an immediate release layer and a controlled release layer.

JAEGER does not address multi-layered tablets in general terms but specifically discloses a three-layered tablet which appears to comprise an outer immediate release layer and two inner controlled release layers. In addition to differing from the tablet of Example 2 of JAEGER in that it is only a bi-layered tablet which does not comprise an immediate release layer, the bi-layered tablet of instant claim 150 comprises at least one second drug (in a controlled release layer) selected from decongestants, expectorants, mucus thinning drugs, and antihistamines whereas the tablet of Example 2 of JAEGER comprises only a single drug, i.e., codeine phosphate.

Appellants submit that for at least the foregoing reasons and the additional reasons set forth above, FANARA in view of JAEGER fails to render obvious the subject

matter of present claim 150, even if one were to assume, *arguendo*, that the Examiner has succeeded in establishing a *prima facie* case of obviousness of independent claim 140.

Claim 183

Claim 183 depends from independent claim 180 (through claim 181) and essentially recites that the bi-layered tablet of claim 180 comprises (a) codeine phosphate and (b) at least two of phenylephedrine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin, and pharmaceutically acceptable salts thereof as the at least one second drug.

Appellants fail to see that FANARA and/or JAEGER teaches or suggests corresponding drug combinations, let alone in connection with a disclosure that the therapeutically effective periods of the drugs (b) are to overlap the therapeutically effective periods of drug (a) by at least about 70 %.

Appellants submit that for at least the foregoing reasons and the additional reasons set forth above, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of claim 183.

Claim 193

Claim 193 depends from independent claim 180 and recites that both layers of the bi-layered tablet of claim 180 are controlled release layers.

Appellants note that the disclosure of FANARA which relates to multi-layered tablets appears to be limited to combinations which comprise both an immediate release layer and a controlled release layer.

JAEGER does not address multi-layered tablets in general terms but discloses a three-layered tablet which appears to comprise an outer immediate release layer and two inner controlled release layers. In addition to differing from the tablet of Example 2 of JAEGER in that it is only a bi-layered tablet which does not comprise an immediate release layer, the bi-layered tablet of instant claim 193 comprises at least one second drug (in a controlled release layer) selected from decongestants, expectorants, mucus thinning drugs, and antihistamines whereas the tablet of Example 2 of JAEGER comprises only a single drug, i.e., codeine phosphate.

Appellants submit that for at least the foregoing reasons and the additional reasons set forth above, FANARA in view of JAEGER fails to render obvious the subject matter of present claim 193.

C. Claims 124-127, 154, 158, 196 And 197 Are Not Rendered Obvious By FANARA In View Of JAEGER In Further View Of FINDLAY

Appellants note that claims 124-127, 154, 158, 196 and 197 depend, directly or indirectly, from independent claims 117 (claims 124-127), 140 (claims 154 and 158) and 180 (claims 196 and 197). As set forth above in detail in sections IV.A.2 and IV.B.2 neither of claims 117, 140 and 180 is rendered obvious by FANARA or FANARA in view of JAEGER. Since FINDLAY clearly does not cure any of the deficiencies of FANARA and JAEGER, it is submitted that for this reason alone, the Examiner has failed to establish a *prima facie* case of obviousness of dependent claims 124-127, 154, 158, 196 and 197 over FANARA in view of JAEGER in further view of FINDLAY.

D. Provisional Rejection Of Claims 117-200

Claims 117-200 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable of claims of one or more of co-pending application Nos. 10/736,902, 10/939,351, 11/012,267, 11/115,293 and 11/115,321.

In this regard, it is submitted that these provisional rejections are not submitted for review herein.

Appellants will take appropriate action in this respect, if deemed necessary, once the Examiner has indicated allowable subject matter.

V. CONCLUSION

Appellants respectfully submit that for at least all of the foregoing reasons, the Examiner has failed to establish a *prima facie* case of obviousness of the subject matter of claims 117-200 over FANARA, alone or in combination with JAEGER and FINDLAY. The Board is, therefore, respectfully requested to reverse the Final Rejection, and to allow the application to issue in its present form.

Respectfully submitted,
Viswanathan SRINIVASAN et al.

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Date

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CLAIMS APPENDIX

117. A pharmaceutical dosage form which comprises (a) a first drug which comprises at least one morphine derivative having antitussive activity and (b) at least one second drug, wherein a plasma half-life of the at least one second drug differs from a plasma half-life of the first drug and wherein the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

118. The dosage form of claim 117, wherein the at least one morphine derivative comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

119. The dosage form of claim 118, wherein the first drug comprises at least one of codeine phosphate, dihydrocodeine bitartrate and hydrocodone bitartrate.

120. The dosage form of claim 118, wherein the first drug comprises codeine phosphate.

121. The dosage form of claim 118, wherein the at least one second drug comprises at least one of a decongestant, expectorant, mucus thinning drug, and antihistamine.

122. The dosage form of claim 117, wherein the at least one second drug comprises a decongestant.

123. The dosage form of claim 122, wherein the second drug comprises at least one of phenylepherine, pseudoephedrine and pharmaceutically acceptable salts thereof.

124. The dosage form of claim 118, wherein the at least one second drug comprises an antihistamine.

125. The dosage form of claim 124, wherein the antihistamine comprises at least one of chlorpheniramine, promethazine, carbinoxamine and pharmaceutically acceptable salts thereof.

126. The dosage form of claim 117, wherein the at least one second drug comprises an expectorant.

127. The dosage form of claim 126, wherein the expectorant comprises guaifenesin.

128. The dosage form of claim 117, wherein the plasma half-life of the at least one second drug differs from the plasma half-life of the first drug by at least about 2 hours.

129. The dosage form of claim 118, wherein a plasma half-life of the at least one second drug differs from a plasma half-life of the first drug by at least about 3 hours.

130. The dosage form of claim 117, wherein a plasma half-life of the at least one second drug differs from a plasma half-life of the first drug by at least about 4 hours.

131. The dosage form of claim 128, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 80 % of the period of a plasma concentration within the therapeutic range of the first drug.

132. The dosage form of claim 117, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 90 % of the period of a plasma concentration within the therapeutic range of the first drug.

133. The dosage form of claim 130, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 95 % of the period of a plasma concentration within the therapeutic range of the first drug.

134. The dosage form of claim 117, wherein not more than about 30 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

135. The dosage form of claim 132, wherein not more than about 20 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

136. The dosage form of claim 131, wherein not more than about 10 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

137. The dosage form of claim 118, wherein the dosage form comprises a tablet.

138. The dosage form of claim 137, wherein the tablet is a bi-layered tablet.

139. The dosage form of claim 137, wherein the tablet comprises a matrix which comprises the first drug and has dispersed therein particles which comprise the at least one second drug.

140. A bi-layered tablet which comprises a first layer and a second layer, the first layer comprising a first drug which comprises at least one morphine derivative having antitussive activity, and the second layer comprising at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines, wherein the bi-layered tablet provides a plasma concentration within a therapeutic range

of the at least one second drug over a period which is coextensive with at least about 80 % of a period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

141. The dosage form of claim 140, wherein not more than about 20 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

142. The bi-layered tablet of claim 140, wherein the first layer comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

143. The bi-layered tablet of claim 142, wherein the second layer comprises at least one of phenylepherine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin and pharmaceutically acceptable salts thereof.

144. The bi-layered tablet of claim 141, wherein the tablet comprises at least two of phenylepherine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin and pharmaceutically acceptable salts thereof.

145. The bi-layered tablet of claim 140, wherein the first layer only comprises one or more of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof as active ingredient(s).

146. The bi-layered tablet of claim 140, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 90 % of the period of a plasma concentration within the therapeutic range of the first drug.

147. The bi-layered tablet of claim 140, wherein not more than about 10 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

148. The bi-layered tablet of claim 140, wherein at least one of the first and second layers is an immediate release layer.

149. The bi-layered tablet of claim 148, wherein the first layer is an immediate release layer.

150. The bi-layered tablet of claim 140, wherein both of the first and second layers are controlled release layers.

151. The bi-layered tablet of claim 149, wherein the first layer comprises a total of from about 0.1 mg to about 120 mg of at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

152. The bi-layered tablet of claim 140, wherein the first layer comprises a total of from about 5 mg to about 90 mg of at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

153. The bi-layered tablet of claim 151, wherein the first layer comprises a total of from about 25 mg to about 50 mg of at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

154. The bi-layered tablet of claim 152, wherein the second layer comprises at least one of (i) from about 0.1 mg to about 16 mg of chlorpheniramine maleate or an equivalent amount of at least one other pharmaceutically acceptable salt of chlorpheniramine; (ii) from about 1 mg to about 90 mg of phenylepherine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of phenylepherine; (iii) from about 1 mg to about 240 mg of pseudoephedrine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of pseudoephedrine; (iv) from about 0.1 mg to about 75 mg of promethazine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of promethazine; (v) from about 0.1 mg to about 32 mg of carbinoxamine maleate or an equivalent amount of at least one other pharmaceutically acceptable salt of carbinoxamine; and (vi) form about 1 mg to about 2400 mg of guaifenesin or an equivalent amount of at least one pharmaceutically acceptable salt of guaifenesin.

155. The bi-layered tablet of claim 140, wherein the tablet comprises at least one of (i) from about 1 mg to about 90 mg of phenylepherine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of phenylepherine; and (ii) from about 1 mg to about 240 mg of pseudoephedrine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of pseudoephedrine, and the second layer comprises at least one of an antihistamine and an expectorant.

156. The bi-layered tablet of claim 151, wherein not more than about 20 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

157. The bi-layered tablet of claim 152, wherein not more than about 10 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

158. The bi-layered tablet of claim 154, wherein not more than about 10 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

159. A pharmaceutical dosage form which comprises (a) a first drug which comprises at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof and has a first plasma half-life and (b) at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines and has a second plasma half-life which differs from the first plasma half-life by at least about 3 hours, wherein the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 80 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug.

160. The dosage form of claim 159, wherein not more than about 10 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

161. The dosage form of claim 159, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 90 % of the period over which the dosage form provides a plasma concentration within the therapeutic range of the first drug.

162. The dosage form of claim 161, wherein not more than about 5 % of a total period over which the plasma concentration of the at least one second drug is within the

therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

163. The dosage form of claim 159, wherein the dosage form comprises a multi-layered tablet.

164. The dosage form of claim 159, wherein the dosage form is associated with instructions to administer the dosage form three or fewer times per day.

165. The dosage form of claim 117, wherein the dosage form is associated with instructions to administer the dosage form once or twice per day.

166. A pharmaceutical dosage form which comprises (a) at least one first morphine derivative in a first form or layer and (b) at least one second morphine derivative which is different from the first morphine derivative in a second form or layer which is different from the first form or layer, wherein the dosage form releases the at least one first morphine derivative at least one of over a different period and at a different rate than the at least one second morphine derivative.

167. The dosage form of claim 166, wherein the at least one first morphine derivative and the at least one second morphine derivative are independently selected from codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

168. The dosage form of claim 167, wherein the at least one first morphine derivative and the at least one second morphine derivative comprise at least one of codeine phosphate, dihydrocodeine bitartrate and hydrocodone bitartrate.

169. The dosage form of claim 166, wherein the dosage form comprises codeine phosphate.

170. The dosage form of claim 167, wherein the first form or layer is an immediate release form or layer and the second form or layer is a controlled release form or layer.

171. The dosage form of claim 166, wherein the dosage form is a bi-layered tablet which comprises an immediate release layer and a controlled release layer, which layers independently comprise at least one of codeine, dihydrocodeine, hydrocodone and pharmaceutically acceptable salts thereof.

172. The dosage form of claim 171, wherein the dosage form further comprises at least one additional drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines.

173. The dosage form of claim 171, wherein at least the immediate release layer thereof comprises the at least one additional drug.

174. The dosage form of claim 171, wherein at least the controlled release layer thereof comprises the at least one additional drug.

175. The dosage form of claim 166, wherein the dosage form releases the at least one first morphine derivative over a different period and at a different rate than the at least one second morphine derivative.

176. The dosage form of claim 175, wherein the dosage form releases the at least one first morphine derivative over a different period than the at least second morphine derivative.

177. The dosage form of claim 175, wherein the dosage form releases the at least one first morphine derivative over a first period and the at least one second morphine derivative over a second period and not more than about 30 % of the second period are coextensive with all or a part of the first period.

178. The dosage form of claim 177, wherein there is substantially no overlap between the first and second periods.

179. The dosage form of claim 166, wherein the dosage form releases the at least one first morphine derivative at a different rate than the at least second morphine derivative.

180. A bi-layered tablet which comprises a first layer and a second layer, the first layer comprising a first drug which is selected from codeine and pharmaceutically acceptable salts thereof, and the second layer comprising at least one second drug which is selected from decongestants, expectorants, mucus thinning drugs, and antihistamines, wherein the bi-layered tablet provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the bi-layered tablet provides a plasma concentration within a therapeutic range of the first drug.

181. The bi-layered tablet of claim 180, wherein the first layer comprises codeine phosphate.

182. The bi-layered tablet of claim 181, wherein the second layer comprises at least one of phenylepherine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin and pharmaceutically acceptable salts thereof.

183. The bi-layered tablet of claim 181, wherein the tablet comprises at least two of phenylepherine, pseudoephedrine, chlorpheniramine, carbinoxamine, promethazine, guaifenesin and pharmaceutically acceptable salts thereof.

184. The bi-layered tablet of claim 180, wherein the first layer comprises only one or more of codeine and pharmaceutically acceptable salts thereof as active ingredient(s).

185. The bi-layered tablet of claim 180, wherein the period of a plasma concentration within the therapeutic range of the at least one second drug is coextensive with at least about 80 % of the period of a plasma concentration within the therapeutic range of the first drug.

186. The bi-layered tablet of claim 184, wherein the period of a plasma concentration within a therapeutic range of the at least one second drug is coextensive with at least about 90 % of the period of a plasma concentration within a therapeutic range of the first drug.

187. The bi-layered tablet of claim 180, wherein not more than about 20 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

188. The bi-layered tablet of claim 185, wherein not more than about 20 % of a total period over which the plasma concentration of the at least one second drug is within the therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

189. The bi-layered tablet of claim 186, wherein not more than about 10 % of a total period over which the plasma concentration of the at least one second drug is within the

therapeutic range is outside the period over which the plasma concentration of the first drug is within the therapeutic range.

190. The bi-layered tablet of claim 180, wherein at least one of the first and second layers is an immediate release layer.

191. The bi-layered tablet of claim ~~191~~ 190, wherein the first layer is an immediate release layer.

192. The bi-layered tablet of claim 190, wherein the second layer is an immediate release layer.

193. The bi-layered tablet of claim 180, wherein both of the first and second layers are controlled release layers.

194. The bi-layered tablet of claim 180, wherein the first layer comprises a total of from about 5 mg to about 90 mg of at least one of codeine and a pharmaceutically acceptable salt thereof.

195. The bi-layered tablet of claim 180, wherein the first layer comprises a total of from about 25 mg to about 50 mg of at least one of codeine phosphate.

196. The bi-layered tablet of claim 195, wherein the second layer comprises at least one of (i) from about 0.1 mg to about 16 mg of chlorpheniramine maleate or an equivalent amount of at least one other pharmaceutically acceptable salt of chlorpheniramine; (ii) from about 1 mg to about 90 mg of phenylepherine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of phenylepherine; (iii) from about 1 mg to about 240 mg of pseudoephedrine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of pseudoephedrine; (iv) from about 0.1 mg to about 75 mg of promethazine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of promethazine; (v) from about 0.1 mg to about 32 mg of carbinoxamine maleate or an equivalent amount of at least one other pharmaceutically acceptable salt of carbinoxamine; and (vi) form about 1 mg to about 2400 mg of guaifenesin or an equivalent amount of at least one pharmaceutically acceptable salt of guaifenesin.

197. The bi-layered tablet of claim 195, wherein the first layer comprises at least one of (i) from about 1 mg to about 90 mg of phenylepherine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of phenylepherine; and (ii) from about 1 mg to about 240 mg of pseudoephedrine hydrochloride or an equivalent amount of at least one other pharmaceutically acceptable salt of pseudoephedrine, and the second layer comprises at least one of an antihistamine and an expectorant.

198. The dosage form of claim 120, wherein the second drug comprises at least one drug selected from phenylepherine, pseudoephedrine and pharmaceutically acceptable salts thereof.

199. The dosage form of claim 120, wherein the at least one second drug comprises at least one drug selected from chlorpheniramine, promethazine, carbinoxamine and pharmaceutically acceptable salts thereof.

200. The dosage form of claim 120, wherein the at least one second drug comprises guaifenesin.

EVIDENCE APPENDIX

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

downloaded from the Internet on July 5, 2007 and submitted with Amendment filed July 31, 2007

http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

Glossary

β-DYSTROGLYCAN The α- and β-dystroglycans are the laminin-binding components of the dystrophin–glycoprotein complex, which provides a linkage between the subsarcolemmal cytoskeleton and the extracellular matrix.

ACETYLCHOLINE A neurotransmitter ($C_7H_{17}NO_3$) that is released at autonomic synapses and neuromuscular junctions. It is active in the transmission of nerve impulses and is formed enzymatically in tissues from choline.

AMINOGLYCOSIDES A group of antibiotics (such as gentamicin) that inhibit bacterial protein synthesis and are particularly active against Gram-negative bacteria.

CYTOTOXICITY The properties of a virus, transgene, vector, compound or molecule that are toxic for cells.

CpG ISLAND Genomic regions that are rich in the CpG pattern, are resistant to methylation and are often associated with promoter activity.

DEPENDOVIRUS A single-stranded DNA virus from the family parvoviridae (subfamily parvovirinae), which is dependent on a co-infection with helper adenoviruses or herpes viruses for efficient replication.

DYSTROBREVINS The components of the dystrophin–glycoprotein complex that bind to syntrophin and (indirectly) to the C-terminal of dystrophin. Dystrobrevin-α recruits signalling proteins, such as neuronal nitric oxide synthase.

ELECTROPORATION The application of an electric current to the plasma membrane of a cell, to temporarily open pores or channels through which DNA might pass.

EPISOMES DNA that can replicate autonomously in the cytoplasm of host cells.

EXTRACELLULAR MATRIX In muscle, this is a thin layer (basal lamina) that contains collagen, elastin and fibronectin, which surrounds each muscle fibre. This might act as a semipermeable filter or a selective cellular barrier and is important in regeneration after damage.

F-ACTIN A protein that is involved in the contractile apparatus and the maintenance of the cytoskeleton of myofibres.

HEK-293 CELLS Host cells that generate viral particles following transfection with the rAAV plasmid and the helper plasmid.

IMMUNOGENICITY The properties of a virus, transgene, vector, compound or molecule that provoke an immune response.

MICROBUBBLES Encapsulated gas microbubbles that can be used as drug or gene carriers, which are able to penetrate into the smallest membranes. When exposed to sufficiently high-amplitude ultrasound, the microbubbles rupture and release the drugs and genes that are contained in their encapsulating layer.

MYOBLAST TRANSPLANTATION The implantation of exogenous muscle-progenitor cells into muscle to generate new myofibres or to support existing myofibres.

NEO-ANTIGEN A foreign (transgene) product that is able to stimulate an immune response.

PHARMACOKINETIC PROFILE The characteristics of a drug that determine its absorption, distribution and elimination in the body.

PRE-mRNA SPLICING The removal of introns from the precursor mRNA molecule; the remaining exons are spliced together.

PRESSURIZED ISOLATED-LIMB PERFUSION The introduction of therapeutic agents under pressure in a limb after isolation of the blood circulation by clamping.

PRIMARY MUSCLE-CELL CULTURES Cells that are taken into culture directly from a tissue biopsy. In contrast to cell lines that only contain immortalized cells, these

cultures contain heterogeneous cell populations.

RNaseH Ribonuclease H. An enzyme that cleaves RNA/DNA complexes.

SARCOLEMMA The membrane that encloses a striated muscle fibre.

SPECTRIN A large contractile submembrane protein that, similar to dystrophin, contains an actin-binding domain and a long repeat domain.

SPLICEOSOMAL COMPLEX A large dynamic complex that consists of small nuclear RNA molecules and protein components. It mediates the two catalytic steps of the splicing reaction: the excision of introns from the pre-mRNA and the ligation of the two exon termini.

SYNTROPHINS Peripheral membrane proteins that bind to the C-terminal of dystrophin, which might have a role in the process of synaptogenesis.

TRANSDUCTION The transfer of genetic material into a cell using a viral vector.

TRANSFECTION The transfer of exogenous DNA into a cell.